Congenital Aganglionic Megacolon (**Hirschsprung Disease**)

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History

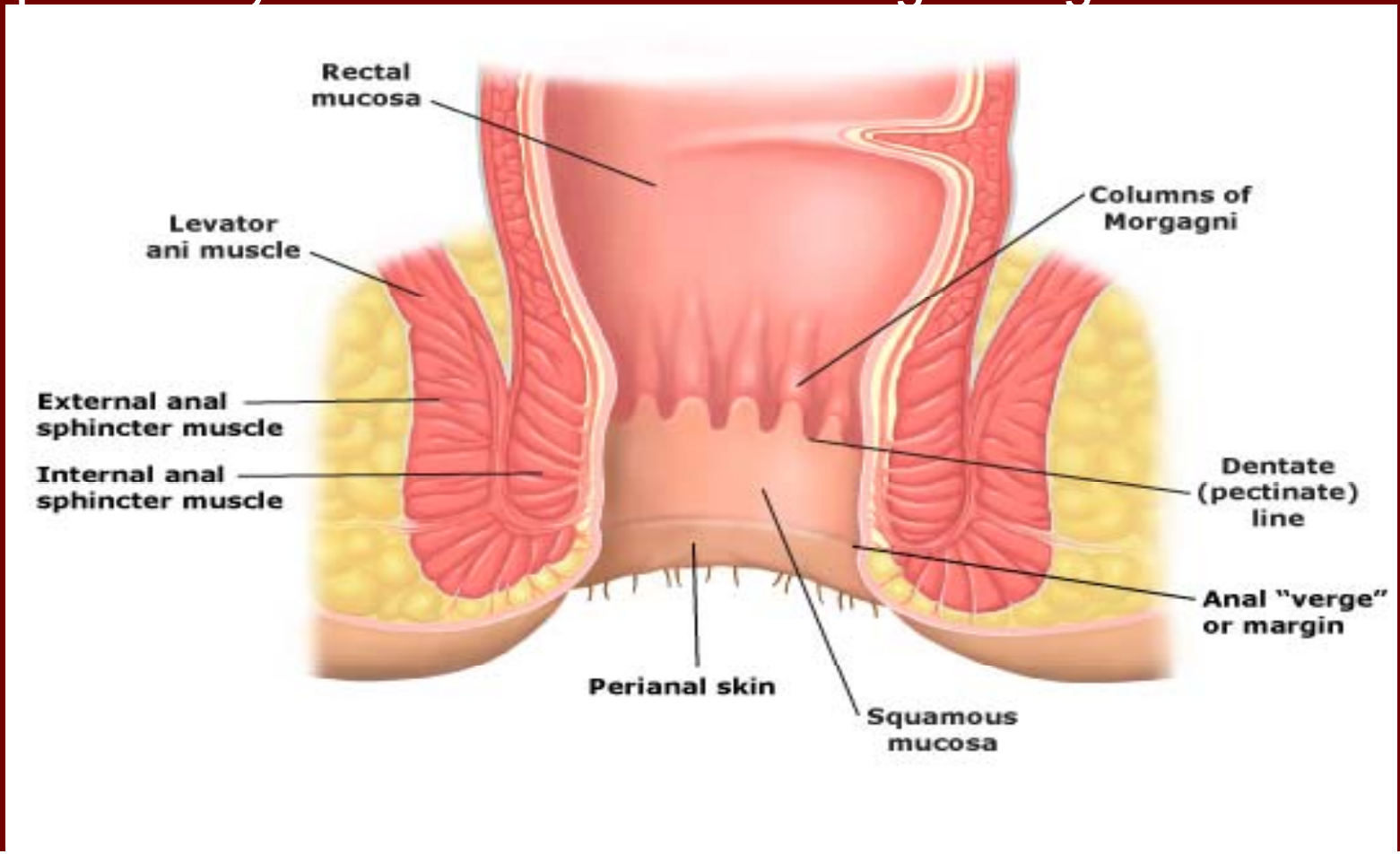
- 1886 – Harald Hirschsprung provided the first detailed description of the disease diagnosed on the autopsy of 2 children
- 1948 – Whitehouse & Zuelzer independently confirmed an absence of ganglion cells in the distal colon of affected individuals
- 1948 – Orvar Swenson performed the first surgery

Topics

- Overview
- Associated Syndromes
- Types
- Pathology
- Genetics
- Clinical Features
- Diagnostic
- Treatment
- Prognosis
- Future Directions

Overview

- Etiology: congenital abnormal innervations of the bowel, beginning in the internal anal sphincter and extending proximally to involve a variable length of gut



Incidence

- 1/5,000 live births
- Most common cause of lower intestinal obstruction in neonates
- Males are affected more often than females (4:1)

Associated Syndromes & Diseases

- Hirschsprung Disease is associated with other congenital defects and diseases:
  - Down,
  - Smith-Lemli-Opitz,
  - Shah-Waardenburg (Pigmentary abnormalities and SN deafness),
  - Cartilage-hair hypoplasia,
  - Congenital hypoventilation (“Ondine curse”) syndrome
  - Urogenital, 5.6%
  - Cardiovascular abnormalities, 4.5%
  - Microcephaly,
  - Mental retardation,
  - Autism,
  - Hydrocephalus,

- Abnormal facies,
- Cleft palate,
- Micrognathia

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Types

- **Ultra short segmental Hirschsprung disease** or internal anal sphincter achalasia
- **Long-segment Hirschsprung disease**

Ultra short Segmental

- Aganglionic segment is limited to the internal anal sphincter
- Involvement includes sigmoid colon and rectum
- Accounts for 90% of the cases
- The clinical symptoms are similar to those of children with functional constipation

Long-Segment

- Begins proximal to the sigmoid colon
- Accounts for 10% of the cases
- Involving the entire colon (total colonic aganglionosis) – 5% of the cases and part of the small bowel
- Rectal motility studies and rectal suction biopsy demonstrate findings of **Hirschsprung disease**

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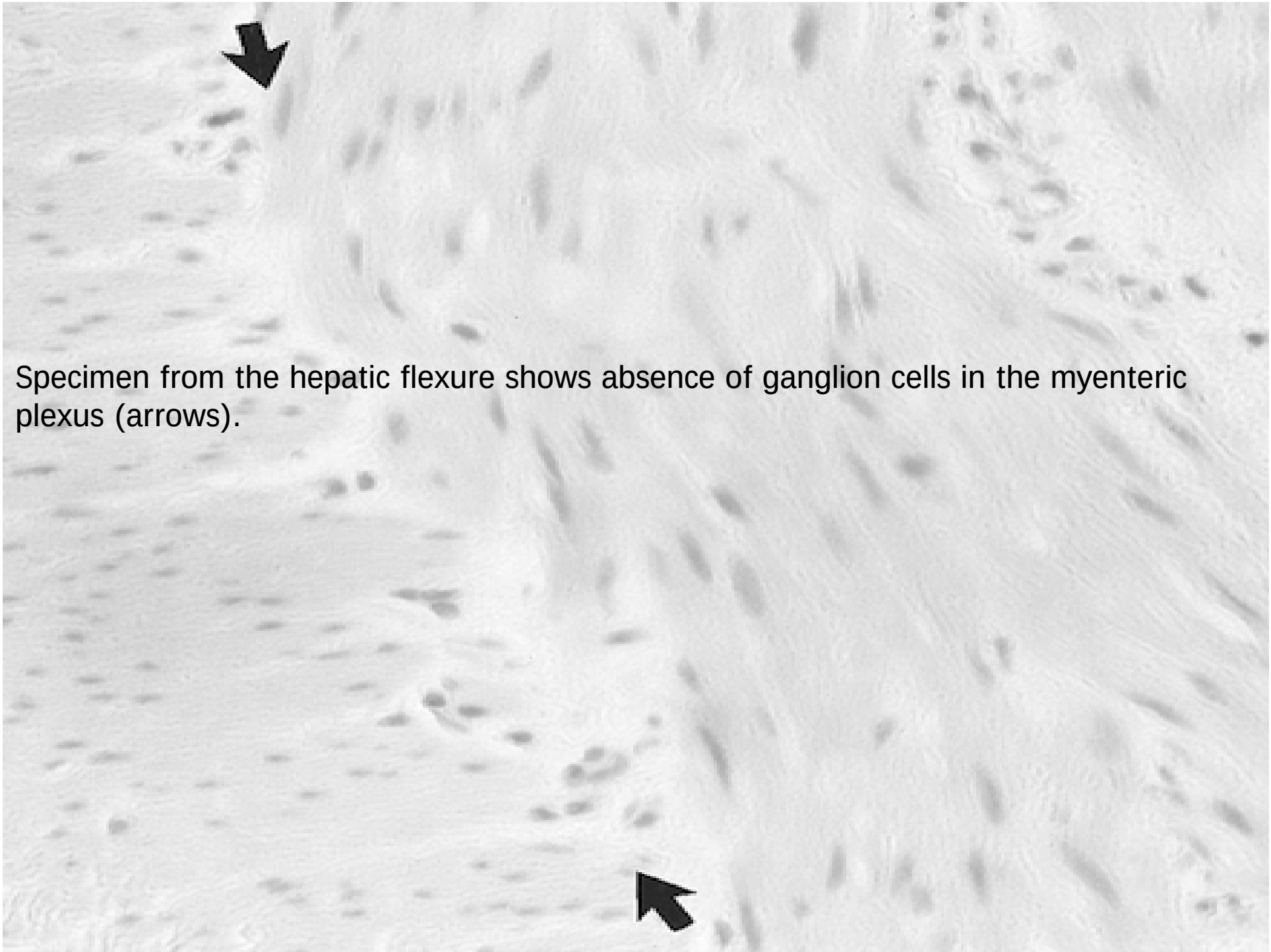
Pathology

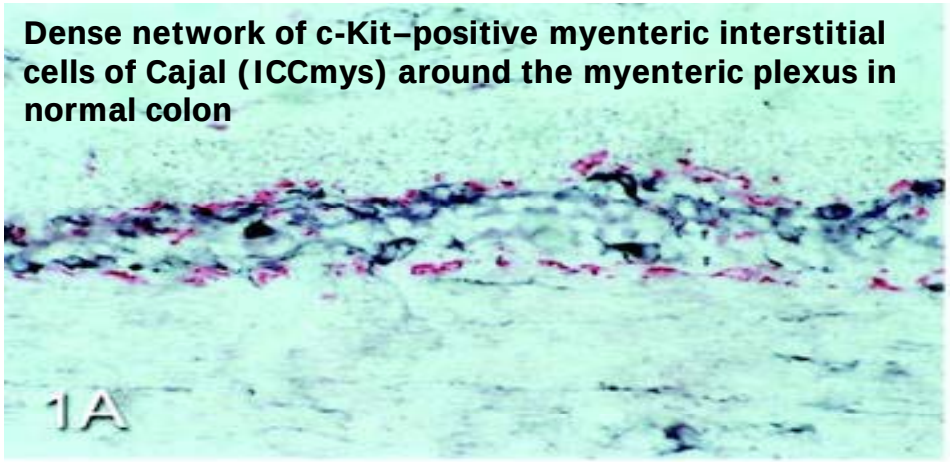
- Absence of ganglion cells in the bowel wall, extending proximally and continuously from the anus for a variable distance.
- A consequence of an arrest of neuroblast migration from the proximal to distal bowel.
- Sporadic with dominant and recessive patterns of inheritance

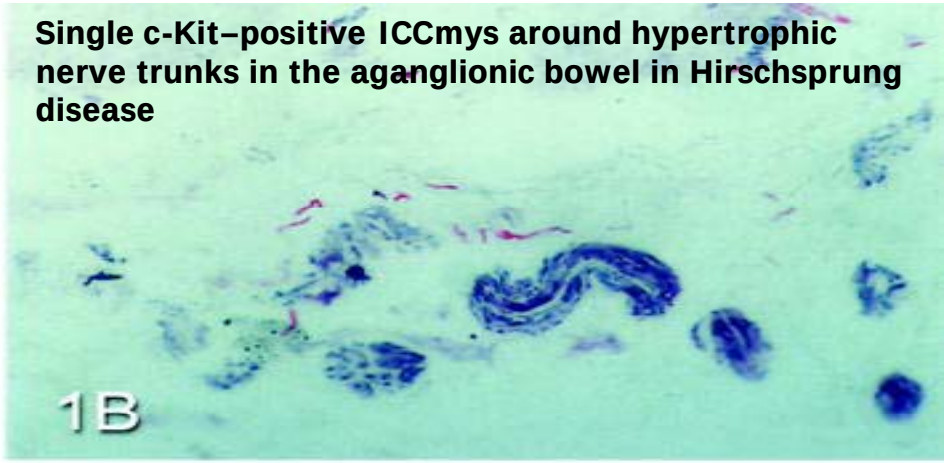
Pathology

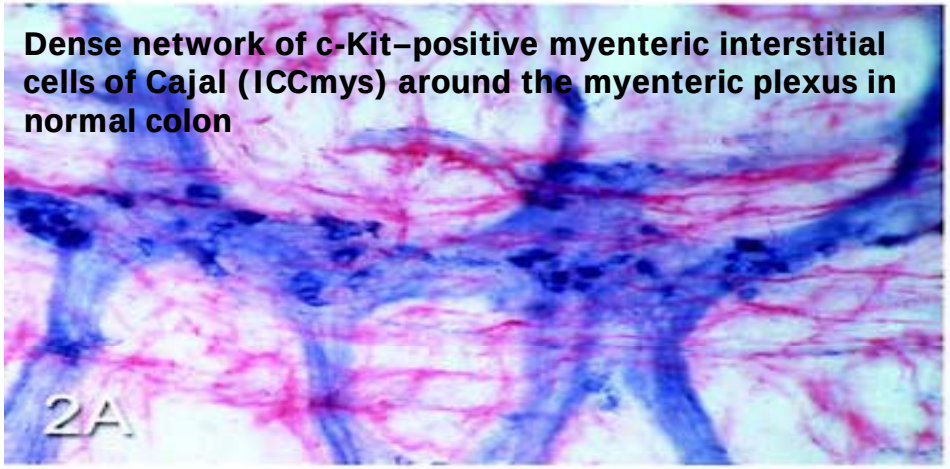
- The aganglionic segment is limited to the recto sigmoid in 75% of patients
- 10%, the entire colon lacks ganglion cells
- Histological:
  - absence of Meissner and Auerbach plexus and hypertrophied nerve bundles with high concentrations of acetyl cholinesterase between the muscular layers and in the submucosa

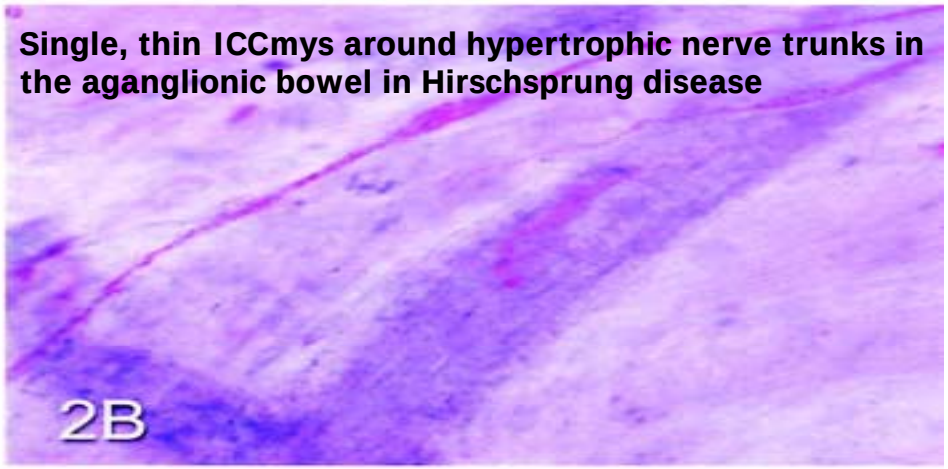


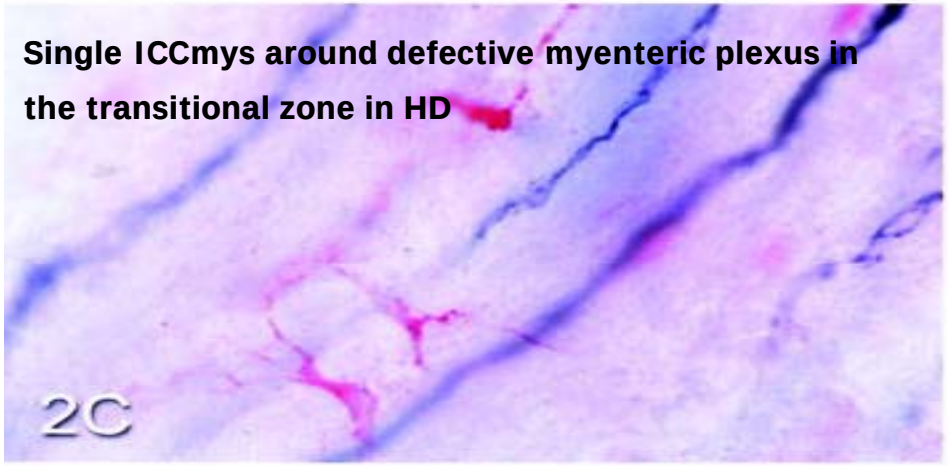
Specimen from the hepatic flexure shows absence of ganglion cells in the myenteric plexus (arrows).

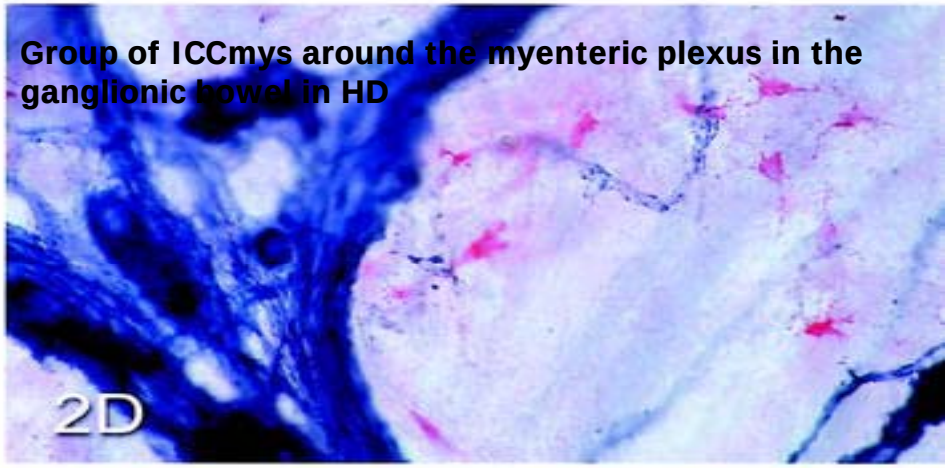

Dense network of c-Kit–positive myenteric interstitial cells of Cajal (ICCmys) around the myenteric plexus in normal colon
1A


Single c-Kit–positive ICCmys around hypertrophic nerve trunks in the aganglionic bowel in Hirschsprung disease
1B


Dense network of c-Kit–positive myenteric interstitial cells of Cajal (ICCmys) around the myenteric plexus in normal colon
2A


Single, thin ICCmys around hypertrophic nerve trunks in the aganglionic bowel in Hirschsprung disease
2B


Single ICCmys around defective myenteric plexus in the transitional zone in HD
2C


Group of ICCmys around the myenteric plexus in the ganglionic bowel in HD
2D

Pathology

- **Ultra short segmental**
  - Ganglion cells are present on rectal suction biopsy, but the rectal motility is abnormal.
- **Long-segment**
  - Usually entire colon is aganglionic

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Genetics

- Genetic defects have been identified in multiple genes that encode proteins of the RET signaling pathway (*RET, GDNF,* and *NTN*) and that are involved in the endothelin (EDN) type B receptor pathway (*EDNRB, EDN3,* and *EVE-1*).
- Syndromic forms of **Hirschsprung disease** have been associated with the *L1CAM, SOX10,* and *SIP1* genes.

Genetics

- The *RET* gene encodes a transmembrane receptor tyrosine kinase and is the major susceptibility gene
- Loss of Function (absence of RET protein function)
- Dominant Negative (the abnormal gene product interferes with functioning of the normal gene product)
- Common in Long-Segment Type

Genetics

- Mutations in Endothelin (EDN) type B receptor pathway are found in approximately 5% of patients
- Absence of the Endothelin B activation leads to abnormal colonization beginning n the region of the cecum
- Inhibits neuronal differentiation
- Associated with short segment

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Clinical Features

- Depend upon the age of presentation and length of aganglionic bowel.
- 40% of individuals are diagnosed in the first 3 months of life.
- 60% of individuals are diagnosed in the first year of life.

Clinical Features

- Begin at birth with the delayed passage of meconium. In 99% of full-term infants, meconium is passed within 48 hr of birth
- Increasing difficulty with the passage of stools, starting in the 1st few weeks of life.
- A large fecal mass is palpable in the left lower abdomen

Hirschsprung Associated Enterocolitis

- Diarrhea is seen in approximately 1 in 4 neonates
- Failure to pass stool leads to dilatation of the proximal bowel and abdominal distention. As the bowel dilates, intraluminal pressure increases, resulting in decreased blood flow and deterioration of the mucosal barrier.
- Stasis allows proliferation of bacteria, which can lead to enterocolitis (*Clostridium difficile, Staphylococcus aureus,* anaerobes, coliforms) with associated sepsis and signs of bowel obstruction.

Hirschsprung Associated Enterocolitis

- Early recognition of before the onset of enterocolitis is essential in reducing morbidity and mortality.
- Intermittent attacks of intestinal obstruction from retained feces may be associated with pain and fever.
- Bowel Perforation occurs in 3-5%
  - Appendix and proximal colon
  - More common in long segment

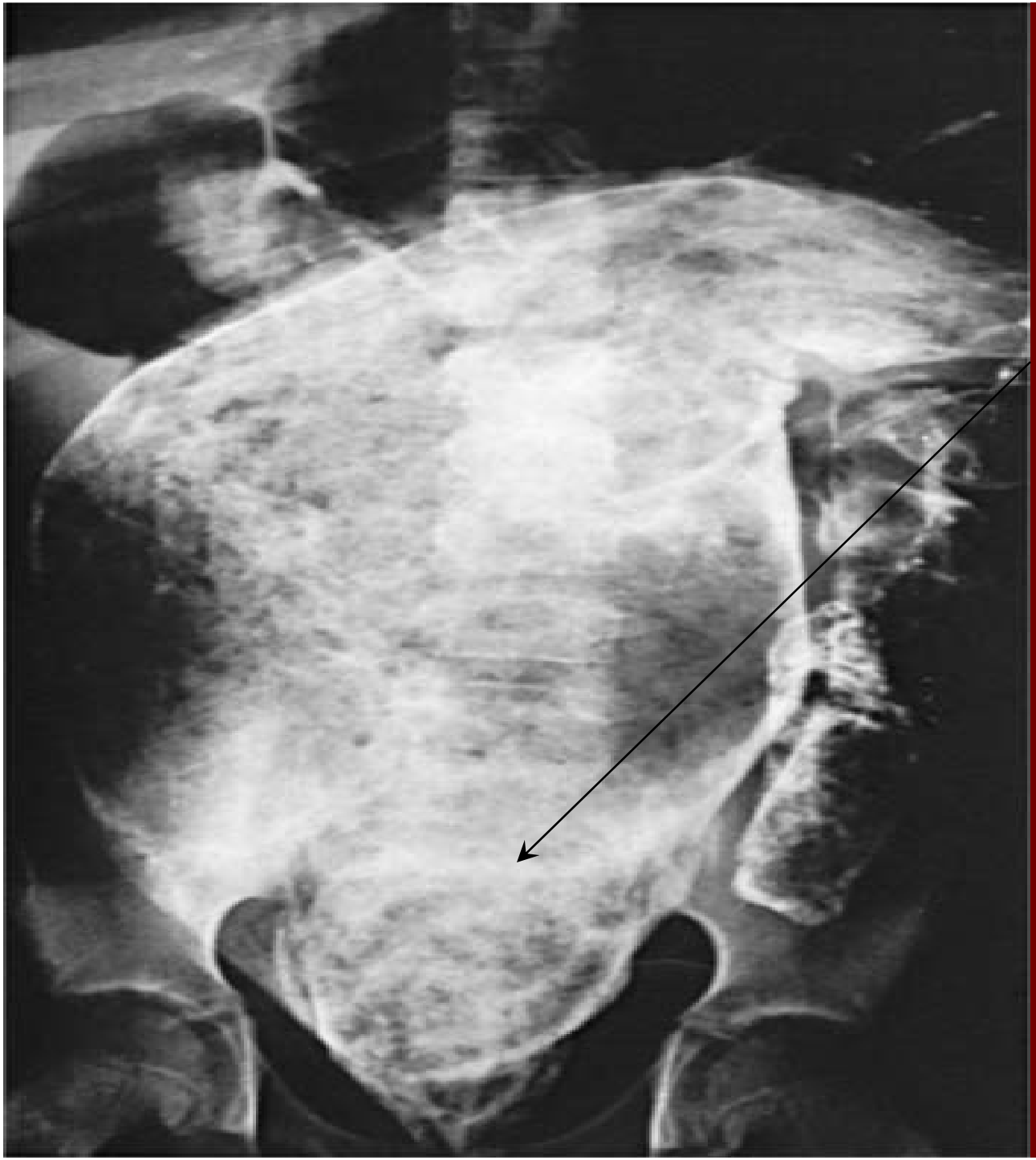
Clinical Features

- P/R – normally placed anus, rectal vault is empty of feces, “finger in glove sensation” (rectal mucosa remains snug to the examiners finger).
- Rectal examination demonstrates normal anal tone and is usually followed by an explosive discharge of foul-smelling feces and gas.
- The stools, when passed, may consist of small pellets, be ribbon-like, or have a fluid consistency.
- Chronic constipation

Clinical Features

- Less commonly:
  - Failure to thrive,
  - Hypoproteinemia from a protein-losing enteropathy
  - Anemia

VARIABLE	FUNCTIONAL (ACQUIRED)	HIRSCHSPRUNG DISEASE
EXAMINATION		
Abdominal distention	Uncommon	Common
Poor weight gain	Rare	Common
Anal tone	Normal	Normal
Rectal examination	Stool in ampulla	Ampulla empty
Malnutrition	None	Possible



Enormous dilatation of the rectum and distal colon is typical of acquired functional megacolon.

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Diagnosis

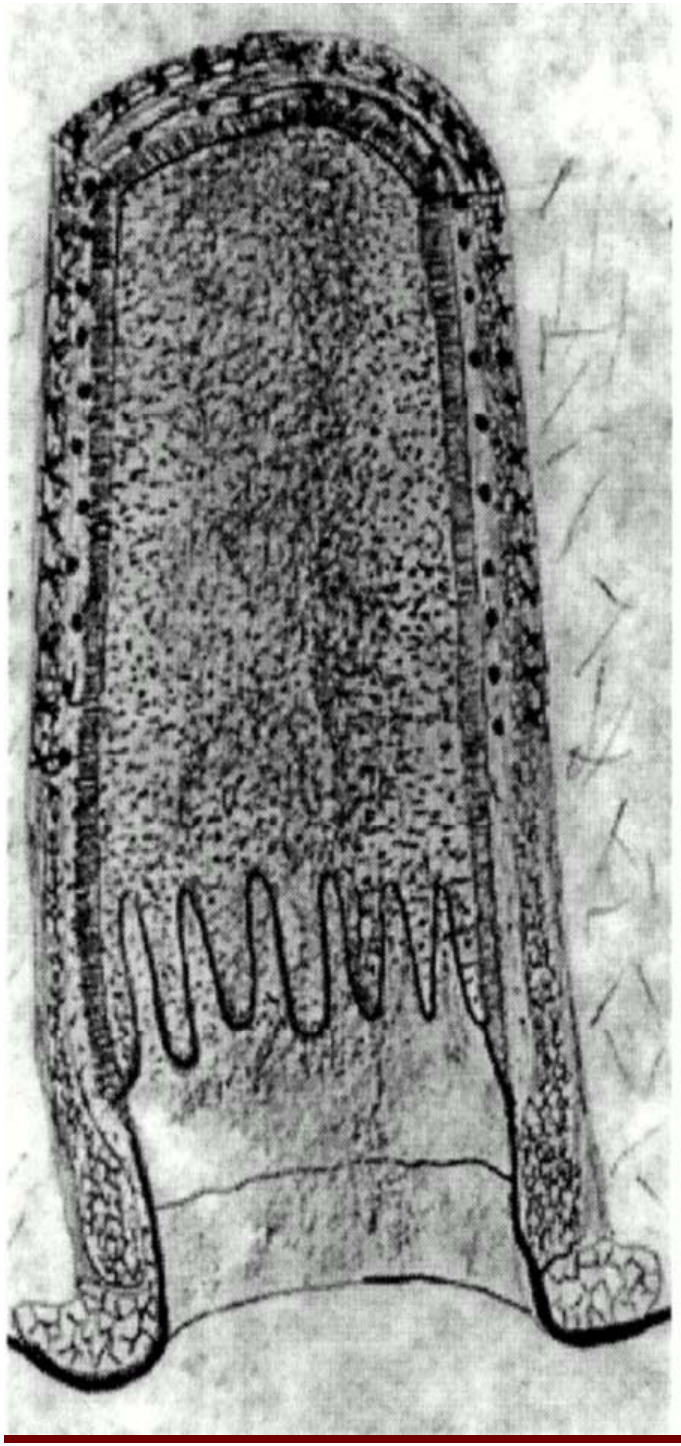
- Abdominal X-rays
  - Loops of distended intestine and may show a paucity of air in the rectum
- Easiest and most reliable indicators
  - Rectal suction biopsies
  - Rectal manometry
- Rectal suction biopsies are the **procedure of choice** and should be performed no closer than 2 cm to the dentate line to avoid the normal area of hypoganglionosis at the anal verge.

Rectal Suction Biopsy

- Specimen
  - Adequate sample of submucosa to evaluate for the presence of ganglion cells.
  - Stained for acetyl cholinesterase, which may facilitate interpretation.
  - Large number of hypertrophied nerve bundles that stain positively for acetyl cholinesterase with an absence of ganglion cells.
  - Full-thickness rectal biopsy can be performed at the time of surgery to confirm the diagnosis and level of involvement.

Histology

- **Ultra short segmental**
  - Ganglion cells are present on rectal suction biopsy.
- **Long-segment**
  - The extent of aganglionosis can be determined accurately by biopsy at the time of laparotomy.



Is the biopsy from the appropriate site? → No → Re-biopsy

Segment of Hypoganglionosis Exists normally in the Submucosal plexus Just above the dentate line

↓ Yes

Is the biopsy adequate? → No → Re-biopsy

↓ Yes

Are ganglion cells present? → Yes → ???

↓ No

Are hypertrophic nerves present? → Yes → HSCR

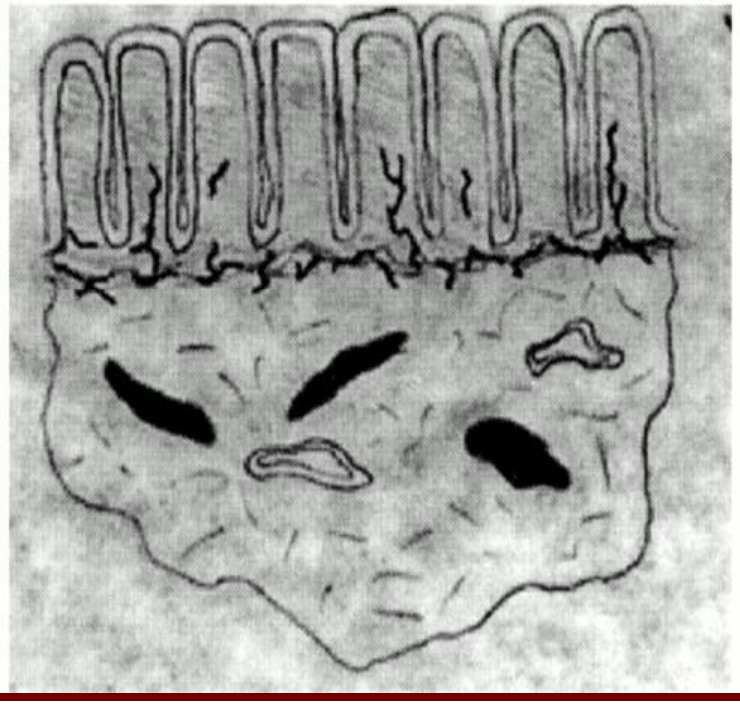
No ↓

AChE stain → Positive → HSCR

↓ Negative

More sections

Re-biopsy?

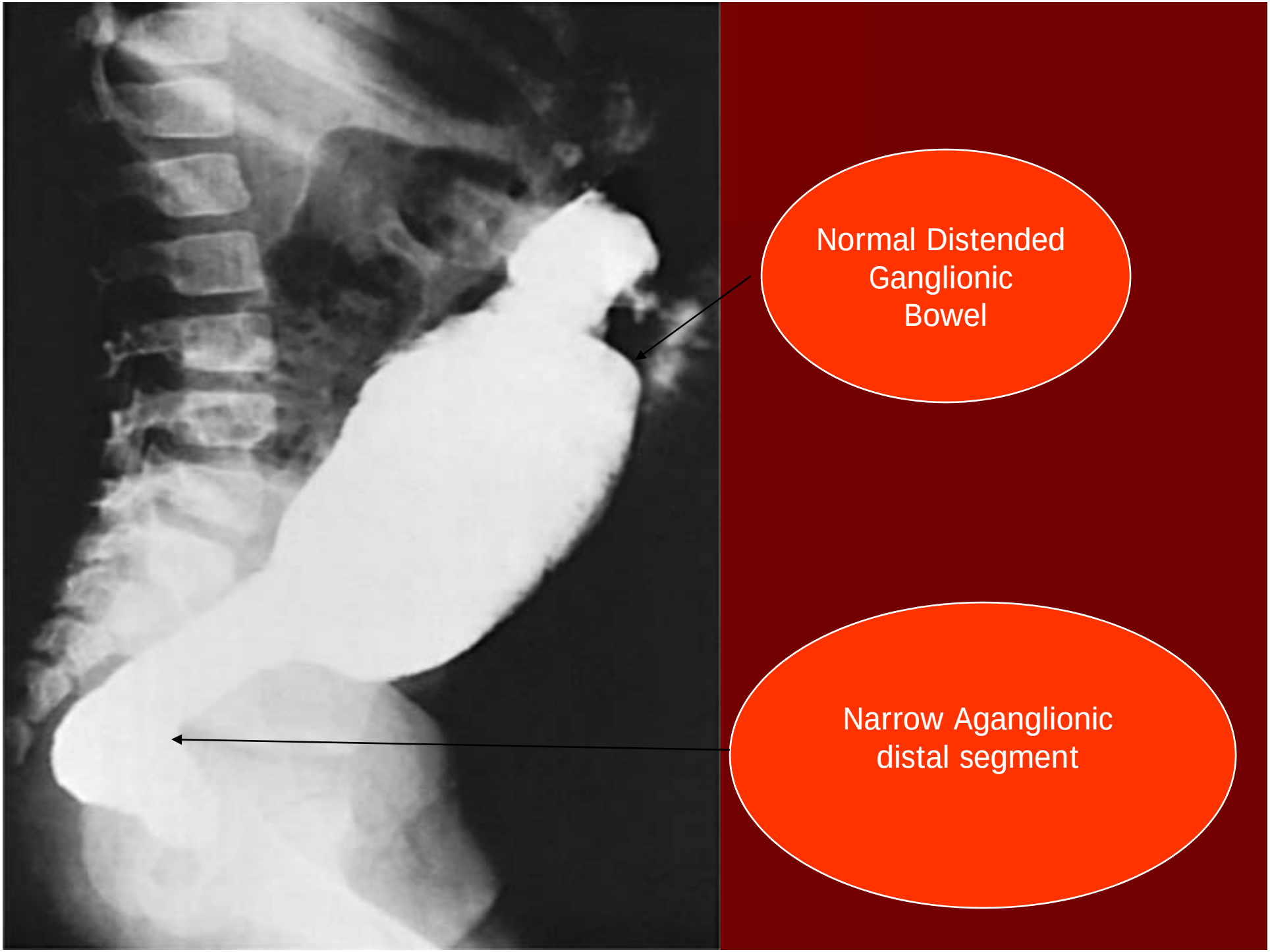


Radiological Diagnosis

- Barium Enema
- Based on the presence of a transition zone between normal dilated proximal colon and a smaller-caliber obstructed distal colon caused by the non-relaxation of the aganglionic bowel.
- The transition zone is not usually present before 1–2 wk of age and, on a radiograph, is a funnel-shaped area of intestine between the proximal dilated colon and the constricted distal bowel.

Radiological Diagnosis

- Barium:
  - Twenty-four hr delayed films are helpful
  - Significant barium is still present in the colon, it increases the suspicion even if a transition zone is not identified.


Normal Distended
Ganglionic
Bowel
Narrow Aganglionic
distal segment

Barium Enema

- Useful in determining the extent of aganglionosis before surgery and in evaluating other diseases that present as lower bowel obstruction in a neonate.
- **Long-segment**
  - Radiologic studies are difficult to interpret because no colonic transition zone can be identified.

Anorectal manometry

- Accuracy of this diagnostic test is >90%, but the test is technically difficult to perform in young infants.
- An equivocal or paradoxical response requires a repeat motility or rectal biopsy.
- **Ultra short segmental**
  - Rectal motility is abnormal even though ganglion cells are present on rectal suction biopsy.

Anorectal manometry

- Measures the pressure of the internal anal sphincter while a balloon is distended in the rectum
  - Normal individuals:
    - Rectal distention initiates a reflex decline in internal sphincter pressure.
  - Hirschsprung patients:
    - pressure fails to drop or there is a paradoxical rise in pressure with rectal distention.

VARIABLE	FUNCTIONAL (ACQUIRED)	HIRSCHSPRUNG DISEASE
Anorectal Manometry	Distention of the rectum causes relaxation of the internal sphincter	No sphincter relaxation or paradoxical increase in pressure
Rectal biopsy	Normal	No ganglion cells, increased acetyl cholinesterase staining
Barium enema	Massive amounts of stool, no transition zone	Transition zone, delayed evacuation (>24 hr)

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Treatment

- Temporary colostomy and wait until the infant is 6–12 mo old to perform definitive repair
- Enterocolitis
  - Rectal decompression tube with saline washes
  - IV antibiotics
- Operative intervention
  - 3 procedures

Operative Procedures

- Swenson
  - Excise the aganglionic segment and anastomose the normal proximal bowel to the rectum 1–2 cm above the dentate line.
  - Technically difficult
- Duhamel
  - Create a neorectum, bringing down normally innervated bowel behind the aganglionic rectum. The neorectum created in this procedure has an anterior aganglionic half with normal sensation and a posterior ganglionic half with normal propulsion.

Operative Intervention

- Boley
  - Endorectal pull-through procedure
    - stripping the mucosa from the aganglionic rectum and bringing normally innervated colon through the residual muscular cuff, thus bypassing the abnormal bowel from within.
    - successful laparoscopically
    - **treatment of choice**

Treatment

- **Ultrashort segmental**
  - Excision of a strip of rectal muscle usually leads to a more regular bowel pattern.
- **Long-segment**
  - The extent of aganglionosis can be determined accurately by biopsy at the time of laparotomy.
  - When the entire colon is aganglionic, often together with a length of terminal ileum, ileal-anal anastomosis is the treatment of choice, preserving part of the aganglionic colon to facilitate water absorption, which helps the stools to become firm.

Prognosis

- The prognosis of surgically treated H**irschsprung disease** is generally satisfactory
- Achieve fecal continence
- Postoperative problems
  - recurrent enterocolitis,
  - stricture,
  - prolapse,
  - perianal abscesses,
  - fecal soiling,
  - Some children will require myectomy or a redo pull-through procedure.

Future Directions

- Neuromuscular disorders could be truly cured by restoration or replacement of missing or dysfunctional ganglia with healthy ganglia
- CNS-Derived neural stem cells have been transplanted to the gut where they formed neurons and improved GI function
- Gut specific neural stem cells
- The nNOS “knockout” mouse, pyloric stenosis
- Limiting factors:
  - Post-transplant survival of the ENS precursors remains a critical limiting factor

Thank You